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TOPICAL REVIEW

Programming of maternal and offspring disease: impact of growth restriction, fetal sex and transmission across generations

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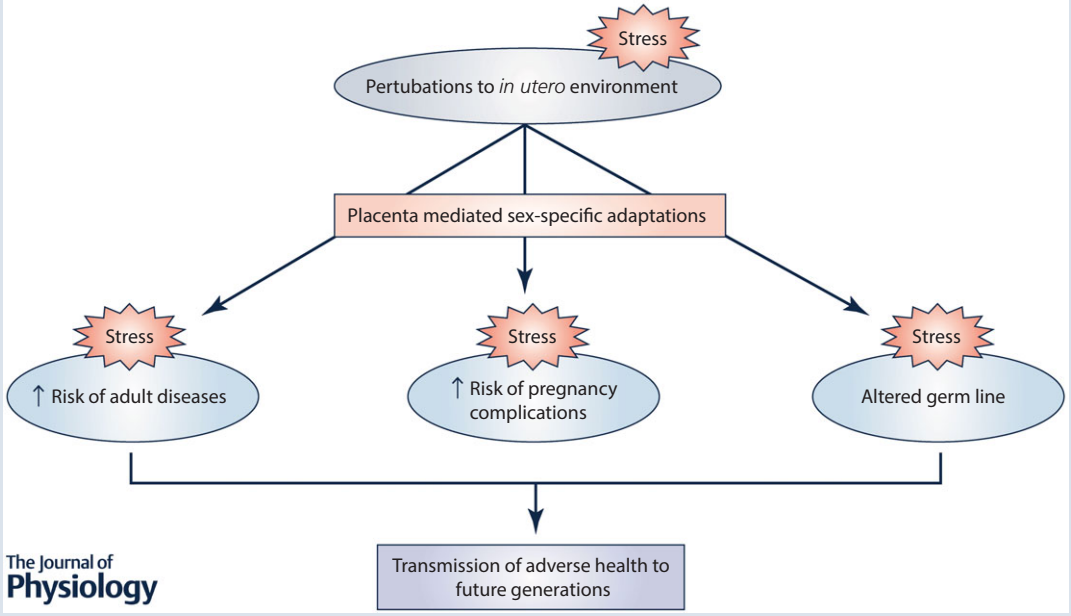

Abstract Babies born small are at an increased risk of developing myriad adult diseases. While growth restriction increases disease risk in all individuals, often a second hit is required to unmask 'programmed' impairments in physiology. Programmed disease outcomes are demonstrated more commonly in male offspring compared with females, with these sex-specific outcomes

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partly attributed to different placenta-regulated growth strategies of the male and female fetus. Pregnancy is known to be a major risk factor for unmasking a number of conditions and can be considered a 'second hit' for women who were born small. As such, female offspring often develop impairments of physiology for the first time during pregnancy that present as pregnancy complications. Numerous maternal stressors can further increase the risk of developing a maternal complication during pregnancy. Importantly, these maternal complications can have long-term consequences for both the mother after pregnancy and the developing fetus. Conditions such as preeclampsia, gestational diabetes and hypertension as well as thyroid, liver and kidney diseases are all conditions that can complicate pregnancy and have long-term consequences for maternal and offspring health. Babies born to mothers who develop these conditions are often at a greater risk of developing disease in adulthood. This has implications as a mechanism for transmission of disease across generations. In this review, we discuss the evidence surrounding long-term intergenerational implications of being born small and/or experiencing stress during pregnancy on programming outcomes.

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Abstract figure legend Sex-specific fetal programming and the transgenerational transmission of diseases. Perturbations of the fetal environment during critical periods of development can have many consequences in postnatal life. This is primarily regulated by the placenta, which is known to respond to stressful stimuli in a sex-specific manner. Individuals exposed to suboptimal conditions *in utero* are programmed for various diseases including cardiovascular and metabolic diseases. Females programmed during fetal life have increased risk of developing pregnancy complications. The germ cells of exposed individuals may also be compromised. Together, they contribute to an adverse fetal environment and places the next generation of offspring at risk of adverse health. Importantly, stress is known to exacerbate these programmed outcomes during fetal and postnatal life.

Introduction

The lifelong health of an individual is determined by the cumulative experiences he or she is exposed to throughout life. Often, the earlier an event occurs in an individual's life, the greater the impact it has on long-term health outcomes. This is particularly true of fetal development, with numerous studies demonstrating that adult disease may be influenced by events that occurred in the womb (Gluckman *et al.* 2007). While some individuals who are 'programmed' to have an increased risk of disease will develop symptoms despite living a healthy lifestyle, others may develop disease only after a 'second hit' such as chronic exposure to factors including smoking, consumption of high-salt or high-fat diet, excessive consumption of alcohol and by living a sedentary lifestyle. An extremely common and severe 'second hit' for females, known to unmask a variety of conditions in adult life, is pregnancy. In fact, pregnancy is the greatest physiological 'stress test' that a woman can experience in her life. With large physiological adaptations occurring during normal pregnancies (Torgersen & Curran, 2006; Weissgerber & Wolfe, 2006), factors that negatively impact maternal physiology can have profound implications for the success of the pregnancy. Women who are programmed to have an increased risk of disease prior to pregnancy may develop disease for the first time during pregnancy. Common pregnancy complications include conditions such as pre-eclampsia, gestational diabetes and hypertension, as well as thyroid, liver and kidney diseases (Williams, 2003; Joshi *et al.* 2010; Steegers *et al.* 2010; Acharya *et al.* 2013). Women who develop these diseases during pregnancy may be at greater risk of disease long after the completion of the pregnancy. The fetus that developed in the womb may also have been exposed to suboptimal conditions and may be programmed to develop disease in later life. This potentially leads to the transgenerational transmission of disease.

This review will focus on the consequences of being born small due to uteroplacental insufficiency, the most common cause of growth restriction in Western society. We will discuss how females who were born small are at an increased risk of pregnancy complications and will consider how this may result in the trans-generational transmission of programmed disease. In addition, to understand the mechanisms involved, we will consider outcomes following experimentally induced uteroplacental insufficiency in a rat model of intra-uterine growth restriction that induces offspring outcomes commonly observed following many different pregnancy perturbations.

Programming of adult diseases

The fetal origins of adult disease hypothesis was first described by David Barker, who proposed that disruptions to the intrauterine environment during fetal development have the potential to 'program' increased risks for developing disease during adulthood (Barker, 1994). This concept was put forward when Barker and his colleagues studied the birth and death records of 4654 men born in Hertfordshire and identified that low weight at birth and at 1 year of age was associated with increased mortality from ischaemic heart disease (Barker *et al.* 1989*a*,*b*). Subsequent epidemiological and experimental studies have been able to further expand upon this observation and there is now strong evidence associating low birth weight with increased vulnerability to the development of a wide array of adult diseases (McMillen *et al.* 2005; Gluckman *et al.* 2007; Warner *et al.* 2010). Increased understanding that the early postnatal environment also has important consequences for later health has resulted in the field of developmental origins of health and disease (DOHaD).

Low birth weight is commonly used as a surrogate marker of intrauterine growth restriction (Moritz *et al.* 2009). It is defined as having a birth weight below the 10th percentile of weight for gestational age or below 2.5 kg at term, and accounts for ∼10% of births in the Western world (Martin *et al.* 2011, 2013). The clinical pattern of growth restriction varies depending on the nature of the causative factor, the stage of gestation in which it occurs, and the duration of the intrauterine insult (Lin & Santolaya-Forgas, 1998; Gluckman & Hanson, 2004; Morrison, 2008). A sub-optimal *in utero* environment can be caused by factors such as genetic predisposition, maternal malnutrition, smoking, alcohol consumption, drug abuse and stress, all of which can individually contribute to impaired fetal growth (Lin & Santolaya-Forgas, 1998). Maternal under-nutrition is the predominant cause of growth restriction in developing countries while in Western society, intrauterine growth restriction is largely attributed to uteroplacental insufficiency during late gestation (Henriksen & Clausen, 2002). Uteroplacental insufficiency impairs blood flow through the uterine vessels and placenta, which in turn compromises the supply of oxygen and nutrients to the fetus (Henriksen & Clausen, 2002), and is responsible for approximately 30% of the total cases of fetal growth restriction (Nardozza *et al.* 2012).

Numerous researchers have used sheep models to investigate the role of placental insufficiency in long-term disease outcomes (reviewed by Morrison, 2008). In the sheep, placental insufficiency is induced by removal of placentation sites (carunclectomy) prior to mating or injection of microspheres in late pregnancy (Robinson *et al.* 1979; Cheung *et al.* 2004). The use of microspheres allows for specific stages of gestation to be investigated. These models have been very useful to study the effects of placental insufficiency on fetal development and function (Zhang *et al.* 2015). While the sheep is a robust model for studying long-term physiological outcomes in the programming field, studies are costly and time consuming due to their size and the long gestation period. As a result rodents are frequently used to model this condition and uteroplacental insufficiency can be induced by bilateral ligation of uterine blood vessels, which impedes nutrient and oxygen delivery to the developing fetus. First developed to study the role of uterine blood supply in fetal growth (Wigglesworth, 1974), this is now a widely used technique to induce uteroplacental insufficiency and fetal growth restriction and is particularly useful for studies examining long-term outcomes in offspring throughout the complete life course. We have established a model in Wistar–Kyoto rats in which surgery is performed on day 18 of a 22-day pregnancy to replicate the late gestational onset of uteroplacental insufficiency commonly observed in humans. Our rat model, using bilateral uterine vessel ligation surgery, is known to cause disruption to the intrauterine environment resulting in offspring being consistently 10–15% lighter than control counterparts (Wlodek *et al.* 2005). Although inducing uteroplacental insufficiency through surgery results in sudden onset of the disease, the impact is similar to the diseases identified in humans and mimics their more gradual late gestation insufficiency, including offspring organ deficits, disease predisposition and reductions in birth weight (Table 1). However, as discussed in the following section, disease outcomes are highly dependent upon the sex of the offspring.

Uteroplacental insufficiency results from impaired placental development that often arises as a consequence of maternal diseases such as preeclampsia, hypertension and metabolic diseases (Resnik, 2002). Since the formation of the placenta is an essential feature of mammalian pregnancy, if the spiral arteries fail to migrate into the trophoblast, blood supply to the growing placenta is compromised, potentially resulting in growth restriction and preeclampsia (Nayak & Giudice, 2003). Indeed, human studies have demonstrated associations between placental efficiency and the programming of diseases (Risnes *et al.* 2009; Wen *et al.* 2010). The shape of the placenta in particular can be a marker of maladaptive responses to adverse conditions. In general, a circular placenta is indicative of greater placental efficiency, whereas an oval placenta is indicative of a maladaption to adverse maternal conditions (Eriksson *et al.* 2011; Barker *et al.* 2011). The fact that placental shape reflects impaired fetal development and long-term disease may be explained by the hypothesis that the placenta is polarised from the time of implantation. It has been suggested that the growth of the major axis of the placenta is aligned with the

Table 1. Sex-specific offspring programming outcomes of uteroplacental insufficiency in rats

Offspring disease phenotype	Growth restricted male	Growth restricted female	Growth restricted female during pregnancy
Low birth weight	√ (Wlodek *et al.* 2008)	√ (Gallo *et al.* 2012)	—
Nephron deficits	√6 months (Wlodek *et al.* 2008)	√6 months (Moritz *et al.* 2009)	√4 months (Gallo *et al.* 2012)
Glomerular hypertrophy	√6 months (Wlodek *et al.* 2008)	✗6 months (Moritz *et al.* 2009) √18 months (Moritz *et al.* 2009)	√4 months (Gallo *et al.* 2012)
Cardiomyocyte deficits	√Day 7 (Black *et al.* 2012)	Not characterised	Not characterised
High blood pressure	√6 months (Wlodek *et al.* 2008)	✗5 months (Moritz *et al.* 2009) ✗18 months (Moritz *et al.* 2009)	✗4 months (Gallo *et al.* 2012)
β-cell deficits	√6 months (Siebel *et al.* 2010; Laker *et al.* 2011)	√4 months (Gallo *et al.* 2012)	✗4 months (Gallo *et al.* 2012)
Glucose intolerance	√6 months (Siebel *et al.* 2008; Laker *et al.* 2011)	✗4 months (Gallo *et al.* 2012) ✗12 months (Tran *et al.* 2015)	√4 months (Gallo *et al.* 2012)
Impaired insulin response	√6 months (Siebel *et al.* 2008; Laker *et al.* 2011)	✗4 months (Gallo *et al.* 2012) ✗12 months (Tran *et al.* 2015)	✗4 months (Gallo *et al.* 2012)

Uteroplacental insufficiency in rats results in low birth weight and programs sex-specific offspring dysfunction and deficits that often affect males more than females. Even with an additional hit of ageing, females are generally well protected from the development of adult diseases. However, this protection can be lost due to the physiological demands of pregnancy, and diseases are revealed for the first time even at a relatively young age.

rostro-caudal growth of the fetus whereas growth of the minor axis is associated with nutrient availability (Kajantie *et al.* 2010). As such, when a fetus grows to its maximal size despite poor nutrient availability, the placental diameter is likely to be much greater in its major axis than its minor axis. This may in turn impair placental efficiency and lead to programmed disease outcomes. Eriksson *et al.* studied the relationship between placental dimensions and later hypertension, revealing that males often compensate for impaired placentation by expanding the placental surface across its minor axis (Eriksson *et al.* 2010). The fact that this relationship was only evident in males suggests that the placentas of males and females respond differentially to adverse events during pregnancy.

Sexual dimorphism in the developmental origins of health and disease

More males are conceived than females but they are less likely to survive to term such that this sex bias is almost absent by birth (Kraemer, 2000). Male fetuses grow at a faster rate than do females and this accelerated growth trajectory makes male fetuses more vulnerable during disturbed pregnancies, with less favourable outcomes occurring throughout the life course of the individual (Eriksson *et al.* 2010; Ben-Haroush *et al.* 2012). When faced with an adverse challenge, males often do not alter their growth trajectories, but instead continue to grow, ultimately attempting to maintain overall size. In contrast, the slower growth pattern of female fetuses provides flexibility for them to adapt to the surrounding environment by investing in long-term survival (Clifton, 2010; Rosenfeld, 2015). These sexually dimorphic adaptations are regulated by the placenta, which is itself a sexually dimorphic organ (Buckberry *et al.* 2014; Myatt *et al.* 2014; Rosenfeld, 2015; Matheson *et al.* 2016). Placentas of male and female human fetuses express vastly different mRNA profiles (Buckberry *et al.* 2014) and rodent models also demonstrate sexually dimorphic placental and fetal responses to pregnancy

perturbations. In mice, maternal dexamethasone exposure or magnesium deficiency reduces fetal weight in both males and females but causes sex-specific changes in placental weight, morphology and the expression of growth factors and placental transporters (Cuffe *et al.* 2011; Schlegel *et al.* 2015). Maternal hypoxia has been shown to dysregulate the expression of nutrient transporters (solute carrier family 2, member 1 (*Slc2a1*) and solute carrier family 38, member 1 (*Slc38a1*)) and growth factors (insulin-like growth factor 1 receptor (*Igf1r*) and insulin like growth factor 2 (*Igf2*)) in placentas of female fetuses only (Cuffe *et al.* 2014). Female-specific placental adaptations similarly occur in rats following exposure to alcohol around conception, with the placentas of female fetuses having increased cell accumulation of glycogen and increased glucose transporter 3 (*Glut3*), kinase insert domain receptor (*Kdr*) and *Igf2* mRNA expression while males had reduced *Igf1r* and *Glut3* expression (Gardebjer *et al.* 2014). Human pregnancies complicated by maternal obesity result in sex-specific impairment of mitochondrial function, although its functional consequences in the placenta are not yet understood (Mele *et al.* 2014; Muralimanoharan *et al.* 2015).

These sex-specific placental adaptations are often associated with male offspring developing adult disease while females are minimally affected. In the mouse model of dexamethasone exposure, only male offspring developed hypertension (O'Sullivan *et al.* 2013). Similarly, periconceptional alcohol exposure programs more severe metabolic phenotypes in male offspring, an effect that is exacerbated following exposure to a high-fat diet in postnatal life (Gardebjer *et al.* 2015). We have extensively studied the sex-specific outcomes in our rat model of uteroplacental insufficiency (Table 1). Male but not female offspring develop increased systolic blood pressure in adult life. This is despite both sexes having decreased nephron number and males (females were not characterised) having a cardiomyocyte deficit early in life (Black *et al.* 2012). Interestingly, glomerular hypertrophy developed in males by 6 months of age but was only evident in females at 18 months (Wlodek *et al.* 2008; Moritz *et al.* 2009). Male offspring also had impaired glucose tolerance and reduced insulin secretion (Siebel *et al.* 2008), which was accompanied by a reduction in pancreatic β-cell mass (Siebel *et al.* 2010; Laker *et al.* 2011). In contrast, females born small had a normal metabolic profile despite having pancreatic deficits. Together, these studies highlight that despite similar structural changes in both sexes (nephron and β-cell deficits), the programmed disease phenotype is only evident in male offspring. While these differences could be attributed to the different growth strategies that male and female fetuses employ *in utero* as we discussed earlier, insults experienced *in utero* have been shown to induce sex-specific changes in hormones in postnatal life that may contribute to sex-specific disease phenotypes (Romano *et al.* 2015). In addition, sex hormones are known to regulate normal physiology and are likely to contribute to differences in programmed disease outcomes between males and females (Ojeda *et al.* 2013).

Pregnancy unmasks programmed disease in susceptible females

Although females are generally less susceptible to programmed disease development, under the physiological demands of pregnancy, various disease states are often unmasked (Table 1). Specifically, female rats born small following uteroplacental insufficiency develop glucose intolerance for the first time during gestation (Gallo *et al.* 2012). Indeed, studies have demonstrated that pregnancy complications such as gestational diabetes and preeclampsia are more prevalent in women that were themselves born small but were otherwise healthy before pregnancy (Zetterström *et al.* 2007; á Rogvi *et al.* 2012). This suggests maternal events or 'second hits' experienced during pregnancy may unmask predispositions to pregnancy complications. Thus it may be that latent programmed phenotypes can subsequently affect the mother either during or after pregnancy, and consequently her offspring (Fig. 1).

In order to further characterise pregnancy adaptations of female rats born small following uteroplacental insufficiency, we conducted a series of physiological measurements (metabolic cage, tail cuff blood pressure, intraperitoneal glucose tolerance test) during pregnancy. Interestingly, the physiological measurements conducted during gestation induced fetal growth restriction in the developing rat, but only when their mothers themselves were small at birth (Gallo *et al.* 2012). This suggests a complex interaction between being born small, physiological adaptations associated with pregnancy and being stressed during pregnancy, which may translate at a population level to the transmission of disease vulnerability across generations. Stress in pregnancy is known to contribute towards myriad pregnancy complications and offspring disease outcomes, but rarely has the birth weight of the mother been considered. These aspects are often considered in isolation and rarely is stress considered a trigger for unmasking pregnancy complications that may result in impaired fetal development and programmed disease outcomes.

Interaction of stress and pregnancy in unmasking disease phenotype in programmed individuals

Numerous reviews have previously discussed how the type of 'stress' (or exposure to 'stress' hormones), the model species used and the timing of exposure all contribute to the type and severity of programmed disease outcomes (Drake *et al.* 2007; Singh *et al.* 2012; Giussani *et al.* 2013;

Table 2. Stress during pregnancy and associated pregnancy complications in humans

Type of stress	Pregnancy complications	References
Exposure to Hurricane Katrina	Induction of labour	Oni *et al.* 2015
	Increased perceived stress	
Death of close relative	Preeclampsia	László *et al.* 2013
	Gestational diabetes	László *et al.* 2015
Obesity during pregnancy	Gestational diabetes	Chu *et al.* 2007
Overweight during pregnancy	Preeclampsia	Dempsey *et al.* 2003
Maternal low birth weight	Preeclampsia	Dempsey *et al.* 2003
	Gestational diabetes	Seghieri *et al.* 2002
Vitamin D deficiency	Preeclampsia	Bodnar *et al.* 2014

Stressful maternal events that can contribute to the development of various pregnancy complications as demonstrated in epidemiological studies.

Moisiadis & Matthews, 2014). Here, we use the term 'maternal stress' to refer to any external factor that acts as a second hit and places additional pressure on an already strained physiological system during pregnancy that can reveal pregnancy diseases (Table 2). The stress encountered following the death of a family member has been shown to increase the risk of preeclampsia (László *et al.* 2013) and the development of gestational diabetes (László *et al.* 2015). Similarly, women exposed to stress encountered through Hurricane Katrina had an increased incidence of pregnancy-induced hypertension and gestational diabetes (Oni *et al.* 2015). Vitamin D deficiency has been shown to increase the risk of severe preeclampsia (Bodnar *et al.* 2014). Furthermore, women who become pregnant at an advance maternal age, have increased risk of stillbirths and preterm delivery (Kenny *et al.* 2013). Maternal low birth weight has also been implicated in the development of gestational diabetes (Seghieri *et al.* 2002). Another study demonstrated that being born small doubles a women's risk of developing preeclampsia. This risk was increased to fourfold if the women were overweight during pregnancy, demonstrating that the additional stress of being overweight exacerbates the preeclampsia risk (Dempsey *et al.* 2003; Oni *et al.* 2015). Furthermore, maternal obesity is correlated to a substantially higher risk of developing gestational diabetes, with the risk increasing with the severity of obesity (Chu *et al.* 2007).

Of interest, while the mechanisms that regulate programmed pregnancy complications are unknown, they are likely to overlap with factors that program disease outcomes in women exposed to external stressors. Thus, women who are at an increased risk of pregnancy complications may have this complication unmasked by exposure to additional stress. This stress response is likely to involve both a systemic physiological stress response and a cellular stress response. The systemic stress response is largely mediated through hormonal and chemical messengers (such as glucocorticoids or oxygen and glucose) that can transfer the stress signal from the site of action to various tissues throughout the body. In the target tissues, a cellular stress response may ensue. Glucocorticoids regulate stress-responsive pathways by binding to the glucocorticoid receptors to regulate gene transcription (Fowden & Forhead, 2015). Similarly, alterations in blood oxygen saturation can regulate transcription of genes including those involved in proliferation through the activation of hypoxia-inducible factors (Semenza, 2014; Guimarães-Camboa *et al.* 2015). In addition, changes in glucose levels can influence fetal outcome by altering cellular glucose uptake and impacting on embryonic adaptive responses via pathway such as hexosamine signalling and O-linked glycosylation (Howerton & Bale, 2014; Pantaleon *et al.* 2015). Studies have also demonstrated that systemic stress can activate cellular stress pathways including but not limited to cellular oxidative stress (Spiers *et al.* 2015). Oxidative stress has been shown to play a major role in the aetiology of multiple pregnancy complications including preeclampsia (Sahay *et al.* 2015) and intrauterine growth restriction (Schneider *et al.* 2015), and is also known to contribute to programmned disease outcomes in offspring (Giussani *et al.* 2012). Oxidative stress is often associated with mitochondrial dysfunction, which has been demonstrated in the placentas of pregnancies complicated by factors such as maternal obesity (Mele *et al.* 2014; Muralimanoharan *et al.* 2015).

Other cellular stress responses include the heat shock response, the unfolded protein response and the DNA damage response (Fulda *et al.* 2010). Studies have demonstrated that cellular stress pathways converge to induce similar cellular outcomes, being predominantly related to cell survival or cell death. One factor central in the regulation of cellular stress is O-linked-*N*-acetylglucosamine transferase (OGT) (Zachara *et al.* 2011). This enzyme is encoded by an X-linked gene that escapes inactivation in the placenta, resulting in higher OGT levels in females compared with males. OGT regulates O-linked glycosylation to control

cellular functions, predominantly related to cellular stress. Of particular importance, OGT has been recognised as a key mediator of sex differences and placental stress responsivity (Nugent *et al.* 2015). Importantly, OGT has been shown to mediate the toxic effects of maternal hyperglycaemia on early embryonic development (Pantaleon *et al.* 2010). Furthermore, OGT has been suggested to play a major role in the sex-specific programming of disease (Howerton & Bale, 2014) and is well characterised as being a significant factor in the regulation of adult diseases such as diabetes (Akimoto *et al.* 2005).

Effects of maternal pregnancy complications on the long-term health of the mother

Pregnancy is likely to be the greatest physiological challenge in a woman's life, and it is unsurprising that adverse health conditions that develop for the first time during pregnancy often manifest as long-term health conditions well after the completion of pregnancy. A study of more than 129,000 births demonstrated that women who had preeclampsia, preterm delivery or babies in the lowest quintile for birth weight had a significantly higher risk of developing ischaemic heart disease in later life. When a pregnancy was complicated by more than one of these factors, maternal risk increased with each additional factor (Smith *et al.* 2001). Other studies have supported these findings in women diagnosed with preeclampsia known to have increased risk of hypertension, ischaemic heart disease, stroke and venous thromboembolism post-pregnancy (Bellamy *et al.* 2007). Hypertensive disorders diagnosed during pregnancy are also correlated with higher prevalence of metabolic syndrome after pregnancy (Hermes *et al.* 2013). Other studies have shown that women who develop gestational diabetes have increased lifetime risk of developing overt diabetes (Kim *et al.* 2002; Damm, 2009) and their health can be further compromised by second hits such as obesity (Lauenborg *et al.* 2005). In a study of over 5000 women, detection of hypothyroidism in early pregnancy strongly predicts subsequent morbidity related to thyroid conditions post-pregnancy, and overt hypothyroidism during pregnancy has also been known to increase risk of later diabetes morbidity sixfold (Männistö *et al.* 2010). Since women born small have heightened risk of developing pregnancy complications and often have more severe disease phenotypes, it is likely that they also have an increased risk of developing long-term diseases that persist post-pregnancy. Rats that were born small and developed glucose intolerance during pregnancy did not have any long-term cardiovascular or metabolic adverse consequences (Tran *et al.* 2012), but it is hypothesised that an additional 'second hit' of maternal stress may have deleterious effects on long-term maternal health (Fig. 1). Thus far, there have not been any human studies linking low maternal birth weight to later-life health outcomes unmasked by pregnancy. Understanding the underlying mechanisms may provide an opportunity for intervention before the onset of pregnancy or immediately following pregnancy, with the aim of preventing the development of overt disease phenotypes in the mother.

Importantly, if maternal health is compromised following a pregnancy, this may impact upon any future pregnancies she experiences. A women who experience spontaneous preterm delivery in her first pregnancy is at an increased risk of preterm delivery in her second pregnancy (Lykke *et al.* 2009). Furthermore, there is an increased risk of preeclampsia, small for gestational age and placental abruption in the second pregnancy (Lykke *et al.* 2009). This study highlights that the earlier the preterm delivery in the first pregnancy, the higher the risk of a pregnancy complication in the second pregnancy. Similarly, intrauterine growth restriction and hypertensive disorders in the first pregnancy are independent risk factors for increased hypertensive disorders in the second pregnancy (Zhang *et al.* 2001). These findings may reflect increased risk of disease in the second pregnancy due to unmasked disease from the first pregnancy. This warrants investigation in future studies.

Pregnancy complications and programmed offspring outcomes: intergenerational programming of disease

Given that pregnancy complications are more common and more severe in women who themselves were exposed to adverse pregnancy conditions *in utero*, the possibility arises of a transgenerational cycle of disease transmission (Fig. 1). Human and animal studies have supported this hypothesis, and maternal complications such as those mentioned above have been shown to program offspring disease. In a cohort study of over 280,000 pregnancies in Sweden, maternal diabetes was associated with increased BMI in male offspring (Lawlor *et al.* 2011). Similar findings have been reported following other pregnancy complications. Women with hypertension during pregnancy gave birth to offspring who had a greater risk for hypertension (Miettola *et al.* 2013). Grandmaternal depression is similarly predictive of early onset depression in youth and interpersonal difficulties, as well as higher rates of depression among their daughters who had children (Hammen *et al.* 2011).

In experimental studies, the nomenclature used for the various generations involved in intergenerational studies often defines the F0 generation as the pregnant mothers exposed to the initial insult, with the offspring of these mothers being the F1 generation, whilst the second generation offspring are termed the F2 generation and so forth for subsequent generations. In our rat model of uteroplacental insufficiency, the reduced nephron endowment previously observed in the males of the F1

generation (Wlodek *et al.* 2008) persisted to the F2 generation during fetal life in the absence of any additional insults, but was restored after birth (Gallo *et al.* 2014). Furthermore, these F2 males presented with high blood pressure and metabolic disturbances (Tran *et al.* 2013; Gallo *et al.* 2014). Another study has demonstrated that maternal bisphenol A (BPA) exposure is implicated in programming glucose intolerance in F1 and F2 male but not female offspring, once again demonstrating sex specificity of programming outcomes (Susiarjo *et al.* 2015). As the F2 glucose intolerance observed in male offspring cannot be attributed to metabolic disturbances of the mother as F1 females were not affected, this is suggestive of transmission through factors other than maternal environment, with the authors attributing it to epigenetic modifications (Susiarjo *et al.* 2015). In addition, maternal obesity in the mice has been shown to cause cardiac dysfunction and hypertrophy in the male offspring (Fernandez-Twinn *et al.* 2012; Blackmore *et al.* 2014). Indeed, maternal obesity has been implicated in many programming outcomes (Mahizir *et al.* 2015).

Numerous studies have demonstrated that stress during pregnancy can program alterations in offspring glucocorticoid production that may reoccur in subsequent generations. In a model where F1 rat offspring and their lactating F0 mother were subjected to social stress (male intruder) from postnatal day 2 to 16, this led to altered social behaviours in the F2 generation, which were accompanied by reduced glucocorticoid levels (Babb *et al.* 2014). F2 rats whose grandmothers were exposed to restraint stress and forced swimming during gestation had a significantly shorter gestational length even if their mothers had a non-stressful pregnancy, and this effect persisted to the F3 generation (Yao *et al.* 2014). Interestingly, the F3 generation was the first generation to be born of lower birth weight after the initial F0 exposure to stress during pregnancy. Of particular importance is that the developing F1 fetus and F2 germ-line (developing within the F1 fetus) were present during the initial insult to the F0 pregnancy, and may have been directly affected by the perturbation. As the F3 generation is the first generation that is not exposed to the initial insult, it can be deduced that the phenotype is truly of a transgenerational nature and suggests that the transmission is at least partially through epigenetic mechanisms (Skinner, 2008).

Intergenerational programming of disease through paternal lineage

Although a large proportion of previous studies have focused on the maternal contributions to programming outcomes in the offspring, recent evidence in animals has indicated the importance of the paternal contribution. We have published that preimplantation blastocysts derived from fathers born small are altered, highlighting a potential pathway to F2 offspring deficits and dysfunction (Master *et al.* 2015). Ng *et al.* were amongst the first to show that paternal obesity in rodents programmed pancreatic deficits in the resultant female offspring through alterations in pancreatic islet genes. The significance of these findings was that they demonstrated non-genetic transmission of disease of a high-fat diet from father to offspring (Ng *et al.* 2010). The same authors later found evidence of premature ageing and chronic degenerative disorders in white adipose tissue and pancreatic islets of females born to fathers that consumed high-fat diets (Ng *et al.* 2014). Male rats born to mothers who were fed a low-protein diet were found to have reduced plasma corticosterone levels and altered behavioural patterns. Interestingly, when these male rats fathered daughters, these F2 females also had reduced corticosterone levels and altered behavioural patterns. In contrast male offspring of these programmed males were unaffected (Reyes-Castro *et al.* 2015). As discussed above, changes in maternal physiology often contribute to long-term outcomes that may impact on the pregnancy and also lactation in the early postnatal period (Siebel *et al.* 2008, 2010). The main advantage of studying programming outcomes through the paternal line is the elimination of confounders associated with the maternal line such as the maternal environment. In the paternal lineage, the maternal environment is eliminated, leaving genetic and epigenetic mechanisms as the predominant likely explanation (Fig. 1). As the sole mediator of disease transmission within the paternal linage is through the germ line, any impairment in the sperm could lead to persistent effects spanning multiple generations (Jiménez-Chillarón *et al.* 2015). One way in which this could occur is through alterations to chromatin or RNA, especially small non-coding RNAs in the sperm (Lane *et al.* 2014; Gapp *et al.* 2014). Importantly, studies have shown that these changes can be induced through environmental influences, with diet-induced paternal obesity causing alternations in the sperm microRNA, which resulted in metabolic dysregulation in the F1 and F2 generation offspring (Fullston *et al.* 2013). In a model of undernutrition, F1 male mice that were undernourished *in utero* gave rise to F2 mice with altered lipogenic genes in their liver, which was attributed to altered patterns of DNA methylation in the *Lxra* locus (Martínez *et al.* 2014). Intriguingly, the same epigenetic change was observed in the sperm of F1 males that gave rise to the F2 progeny, providing compelling evidence that epigenetic modifications in the germ cells of the one generation can persist and be transmitted to the somatic cells of the next generation (Martínez *et al.* 2014). Male mice that were exposed to 6 weeks of chronic stress at various stages of life induced changes in the sperm microRNA environment. When these mice were bred with a normal female, their

offspring had blunted stress responses to a 15 min restraint stress test and also had lower corticosterone levels, and this was observed regardless of whether the father was stressed early or later in life (Rodgers *et al.* 2013). A separate study that investigated the paternal effects of early prenatal stress on neurodevelopmental processes reported a shift in gene expression in the brain from a male-typical to a more female-typical pattern in the F2 male offspring of prenatally stressed fathers. Furthermore, this disrupted masculinisation process was also associated with altered stress responsivity in adulthood (Morgan & Bale, 2011).

An important point to consider in the transgenerational programming of disease through either the maternal or paternal line is the sex-specific adaptations that occur *in utero* that may regulate whether programmed disease can be passed on to subsequent generations. A major confounding factor to consider is the fact that male fetuses exposed to a suboptimal environment are less likely to survive than their female counterparts (Kraemer, 2000). In contrast, female fetuses are likely to have survived the fetal insult, which may result in their developing disease in adulthood and during pregnancy, potentially inducing disease transmission to future generations.

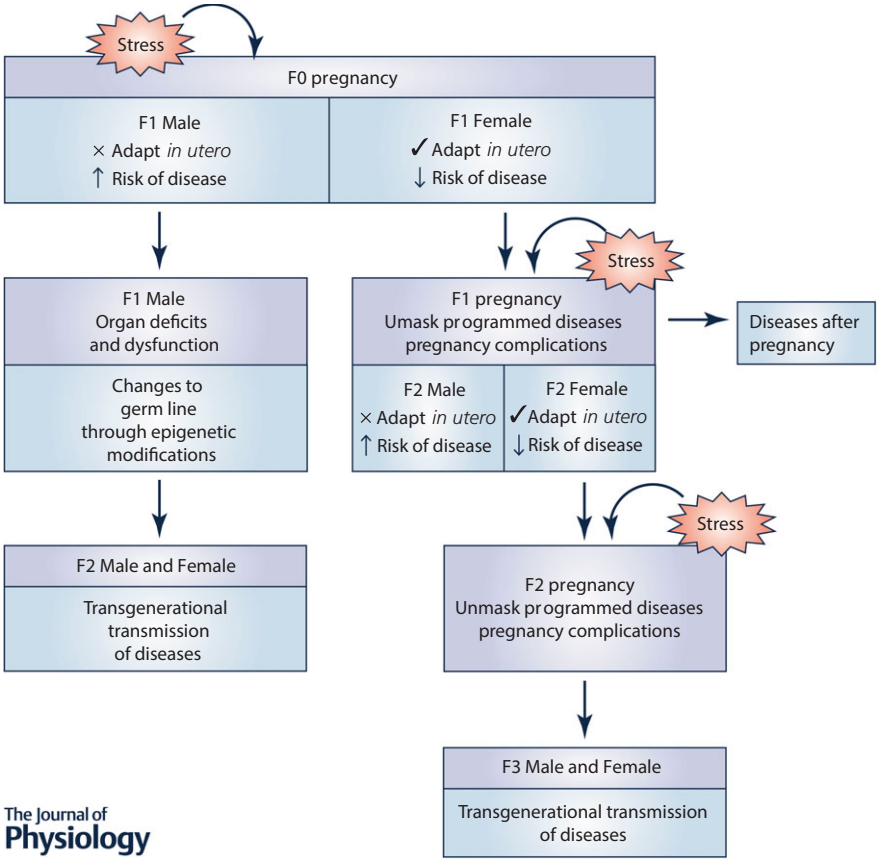

Figure 1. Transgenerational transmission of programmed outcomes through the maternal lineage
Female fetuses generally adapt well to perturbations *in utero* and alter their developmental strategy in accordance with their environment. However, when these F1 females become pregnant, programmed diseases can be unmasked leading to the development of pregnancy complications. This in turn creates a suboptimal intrauterine environment for the developing F2 fetus. Similarly, F2 female fetuses are programmed for adult disease, and when they become pregnant, pregnancy complications may arise leading to programming consequences in the subsequent F3 generation. If the cycle continues, this would result in transgenerational programming of disease that may persist across multiple generations. Furthermore, pregnancy complications impair the long-term health of the mother, and she may experience long-term diseases even after the conclusion of pregnancy. Although the maternal lineage has been thought to be mainly responsible for the transgenerational transmission of disease in the past, recent studies have demonstrated important roles of the paternal lineage. When the developing F1 male fetus is exposed to a suboptimal environment *in utero*, this increases the risk of postnatal organ deficits and dysfunction. This increased susceptibility to adverse health may impact on the germ cells of these males during reproductive age and when they mate with a normal female, the alterations in the germ line may be passed on to the offspring. As the germ cells that give rise to the F2 generation were not present during the initial insult, phenotypes observed in this generation are sufficient to classify this as transgenerational transmission of programmed disease.

Conclusions

Perturbations during fetal development have the ability to program disease in the offspring after birth and into adulthood, and these diseases are more severe and more frequently observed in males. Although females are generally well protected from developing adult diseases, this protection is often lost as a result of the physiological demands of pregnancy. Furthermore, exposure to 'second hits' such as maternal stress during pregnancy can exacerbate the severity of the pregnancy complications. The effects of these complications can be long lasting and maternal health may be compromised well beyond the completion of pregnancy. Hence, studies investigating pregnancy complications should recognise and take into consideration maternal birth weight as a risk factor. Diseases encountered during pregnancy can program the developing fetus for sex-specific offspring diseases that may then be passed on to future generations through either the maternal or the paternal lines. The underlying mechanisms of disease transmission between these two lines are likely to differ. Future studies should aim to uncover the molecular mechanisms of different types of stress and their significance in programming transgenerational disease transmission and long-term maternal health.

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Additional information

Competing interests

None.

Author contributions

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